Predictors and causes of first-line biologic agent discontinuation in rheumatoid arthritis: data from Reuma.pt

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ABSTRACT

Objectives: To assess the discontinuation of first-line biological treatment and to evaluate the reasons and predictors thereof in patients with rheumatoid arthritis (RA) from daily clinical practice.

Methods: RA patients registered in the Rheumatic Diseases Portuguese Register (Reuma.pt) starting treatment with biologic DMARDs (bDMARDs) were included in this prospective observational study. The main outcome was the time to discontinuation (in years) due to any cause. Discontinuation was defined as a 90-day discontinuation of treatment or the occurrence of any switch to another bDMARD during follow-up. Baseline and time-varying sociodemographic and clinical characteristics were tested as possible predictors of discontinuation using multivariable Cox models.

Results: Of the 1,851 RA patients included in the study, 871 (47%) discontinued their first bDMARD. The median overall persistence of the first bDMARD was 5.5 years and the leading cause of discontinuation was inefficacy [N=476 (55%)], followed by adverse events [N=262 (30%)], other causes [N=69, (8%)] and unknown causes [N=64 (7%)]. Patients with a higher HAQ score (more disability) at baseline were more likely to discontinue their first bDMARD [hazard ratio (HR):1.39 (95% CI: 1.17-1.64)], as were patients with a higher number of comorbidities [HR: 1.17 (1.05--1.29)] and patients starting treatment from 2007 onwards [HR:1.89 (1.5-2.38)]. On the contrary, receiving TNFi bDMARD [HR:0.74 (0.57-0.94)] as opposed to non-TNFi was associated with less discontinuation. Expectedly, the higher the DAS28 during follow-up the higher the likelihood to discontinue bDMARD [HR:1.08 (1.06-1.1)]. No other time-varying predictor was found.

Conclusion: In the Portuguese RA population, maintenance of first-line bDMARD was shown to be relatively high. Inefficacy was the leading cause of discontinuation. Features found to predict drug discontinuation (e.g. baseline disability) may contribute to inform clinician's decisions in clinical practice.

Keywords: DMARD; Rheumatoid arhtritis; Anti-tumor necrosis factor-alpha therapy; Biologic disease-modifying anti-rheumatic drugs (bDMARDs)

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory rheumatic disease with an estimated prevalence of 0.7% in the Portuguese adult population[1]. It is associated with progressive joint destruction, leading to significant disability and premature death[2,3]. The pharmacological treatment of RA is aimed at achieving sustained remission and halting disease progression[4,5]. Several randomized clinical trials (RCT) have demonstrated that biologic disease-modifying antirheumatic drugs (bDMARD) are effective in achieving sustained remission and are indicated in patients who responded inadequately to conventional synthetic DMARDs (csDMARD)[6-8].

Prescription patterns in real-world settings are affected in different ways, including the differential

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characteristic of each bDMARD, disease phenotype and other clinical aspects, patient preferences and pharmaco-economic factors[9-11]. Despite their proved efficacy in achieving remission or low disease activity, a significant proportion of bDMARD treated patients do not achieve these therapeutic targets[6,12,13]. On the other hand, bDMARD treatment is associated with possible adverse events[14-16], highlighting the importance of evaluating which patients will benefit the most from bDMARDs and for how long[17].

Drug survival can be interpreted as a composite measure of effectiveness, safety and tolerability[18-25]. Compared to RCTs, 'real-world' (registry-based) observational studies yield relevant data that is easier to translate to clinical practice as they evaluate data from large cohorts with usually longer follow-up periods and include patients that would likely fail to fulfil the stringent inclusion and exclusion criteria of most RCTs[26,27].

Previous observational studies[9,10,13,18,19,25,28-33] have found different bDMARD retention rates and investigated predictors of bDMARD discontinuation. Of note, a gradual increase in drug discontinuation is seen over time mainly due to inefficacy and adverse events (AE)[26]. In a meta-analysis including approximately 200,000 RA patients from different geographic areas[34], factors associated with bDMARD discontinuation were female gender, concomitant use of csDMARDs and glucocorticoid therapy (due to lack of efficacy). Patients (and prescribers) from different countries show inherent particularities (and believes) that influence drug prescription patterns, treatment response and ultimately drug retention[26,35]. It is then relevant to evaluate predicting factors of biologic drug discontinuation in the Portuguese RA population, which has not been done thus far. The aims of this study are to assess the discontinuation of first-line biological treatment in RA patients, and to evaluate the reasons and predictors thereof.

METHODS

STUDY DESIGN AND POPULATION

The Portuguese Rheumatic Diseases Register (Reuma.pt) includes patients with various rheumatic and musculoskeletal diseases (RMD), including RA, from multiple national centers. It was established and is overseen by the Portuguese Rheumatology Society. Data is collected using a standardized online protocol during routine rheumatology clinic visits[36]. We performed a multicentric, prospective observational study including RA patients, diagnosed by the treating rheumatologist, registered in Reuma.pt and starting treatment with bDMARDs from 2001 until January 2016, including TNF inhibitors (TNFi) (adalimumab, certolizumab, etanercept, golimumab and infliximab) and non-TNFi (abatacept, anakinra, rituximab and tocilizumab). Patients under 18 years of age or with concomitant inflammatory rheumatic diseases, except secondary Sjögren's syndrome, were excluded. The baseline visit corresponds to the start of the bDMARD and, thereafter, patients were followed every 6 months. To handle (to the extent possible) information bias, researchers from each center compared data from the central register with local medical records and, when possible, completed missing information in the central database. This study was conducted according to the Declaration of Helsinki and the International Guidelines for Ethical Review of Epidemiological Studies and it was approved by the local ethics committee.

OUTCOME

The outcome of interest was time to discontinuation (in years) of the first bDMARD due to any cause. Drug discontinuation was defined as: a) 90-day discontinuation of treatment (except for rituximab: 18 months)[37] without a subsequent biological administration; b) the occurrence of any switch to another biological agent within 90 days (18 months for rituximab) of the previous administration. Time of exposure was considered from the beginning of therapy with bDMARD until the date of the last administration plus twice the half-life of the specific biologic agent. The reasons for discontinuation were defined and hierarchized (in case more than one was reported) as: i. adverse event (AE); ii. lack or loss of efficacy (hereafter referred as inefficacy); iii. Remission; iv. other causes (pregnancy planning, surgery, patient decision and death); v. Unknown (no reason was reported)

CLINICAL DATA

Clinical data was collected by the treating rheumatologists and included, sociodemographic characteristics: gender, age, education (in years), smoking status (current smoker/non-smoker) and body mass index (BMI), total number of comorbidities (cardiovascular diseases, chronic respiratory diseases, psychiatric illness, chronic kidney disease, Diabetes Mellitus and thyroid dysfunction); laboratory markers: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anti-citrullinated protein anti-

bodies (ACPA) status; RA related variables: age at diagnosis, the time from diagnosis until treatment initiation (in years), year of bDMARD start (<2007/≥ 2007, after the first non-TNFi were licensed for the treatment of RA in Portugal), tender and swollen joint counts (TJC and SJC, respectively), disease activity score (DAS 28-ESR 4 variables)[38], health assessment questionnaire (HAQ)[39], overall pain [visual analogue scale (VAS): 0--10)], patient global and physician global evaluation of disease activity also measured on a 10 cm VAS; specific biologic agent administered and concomitant treatment: csDMARD (yes/no) and oral glucocorticoid therapy (yes/no). Except for sociodemographic characteristics, information on all the remaining variables was collected both at baseline and in each follow-up visit.

STATISTICAL ANALYSIS

Time to bDMARD discontinuation was assessed by Kaplan-Meier survival analysis. In case of loss of follow--up patients were censored at the time of the last recorded bDMARD administration plus twice the half--life of the drug. Multivariable Cox proportional hazards regression (with Efron method to handle tied events) was used to assess the possible association between different clinical and demographic variables and bDMARD discontinuation. Two separate models were built, one assessing baseline variables only and another assessing both time-fixed and time-varying variables (i.e. in the 'time-varying model', variables that inherently change over time were modeled as such: e.g. DAS28-ESR[4] and csDMARD comedication). Variables with p-value<0.20 were selected during the univariable analysis. In the multivariable models, variables were selected if statistically significant (p<0.05) or if clinically relevant (age, gender and year of bDMARD start were forced to the final models), taking both confounding and collinearity into account. All analyses were performed in Stata IC version 12 (StataCorp. 2011)

RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS

In total, 1.851 RA patients were included in the study [n=1.600 females (86.3%); mean age of 58.8±12.6], 709 (38.3%) were treated with etanercept as first biologic, 371 (20%) with adalimumab, 355 (19.2%) with infliximab, 172 (9.3%) with golimumab, 156 (8.4%) with tocilizumab, 59 (3.2%) with rituximab, 15 (0.8%) with anakinra, 11 (0.6%) with certolizumab and 3 (0.2%) with abatacept. As shown in Table I, patients discontinuing the first bDMARD (N=871) had higher baseline HAQ scores (1.54±0.64 vs 1.40±0.65, p=0.001), DAS28-ESR(4) (5.8±1.3 vs 5.5±1.3; p<0.01), ESR (mm/h) (39.6±25.9 vs 35.8±25.5; p<0.05), TJC (11.1±7.6 vs 10.2±7.3; p<0.05), more comorbidities (0.7±0.9 vs 0.5±0.8, p<0.001), and were more likely to receive oral glucocorticoids (70.7% vs 66.3%; p<0.05) compared to those that did not discontinue (N=980).

DRUG SURVIVAL AND REASONS OF DISCONTINUATION

The median overall persistence of the first-line bDMARD was 5.5 years (total time at risk: 6,262 person-years; Figure 1). The most common reasons of discontinuation were inefficacy [N=476 (54.6%)] and AE [N=262 (30%)]. The reasons for discontinuation are detailed in Table II. From the 125 patients with known type of AE, 49 discontinued due to allergic reactions while infection (N=38) was the second most common AE. Other reasons included surgery [N=25 (2.9%)], pregnancy/pregnancy planning [N=7 (0.8%)], remission [N=18 (2.1%)], patient decision [N=14 (1.6%)] and death (unrelated to therapy) [N=5 (0.6%)]. The cause of discontinuation was unknown in 64 patients (7.3%).

PREDICTORS OF DRUG DISCONTINUATION

As shown in Table III, in the baseline model, higher HAQ scores were independently associated with bDMARD discontinuation during follow-up [hazards ratio (HR):1.39 (95%CI: 1.17-1.64)]. Also, more comorbidities at baseline [HR: 1.17 (1.05-1.29)] and starting bDMARD therapy from 2007 onwards [HR:1.89 (1.5-2.38)] were independent predictors of drug discontinuation. On the contrary, receiving TNFi was associated with less discontinuation than treatment with non-TNFi [HR:0.74 (0.57-0.94)]. The only time--varying clinical characteristic predicting discontinuation was DAS28, but with a rather small effect size [HR:1.08 (1.06-1.1)].

DISCUSSION

In this large prospective observational study, we have shown that persistence of first-line bDMARDs amongst

TABLE I. BASELINE CHARACTERISTICS OF THE ENTIRE STUDY POPULATION, COMPARING THOSE WHO DISCONTINUED TO THOSE WHO DID NOT

	All patients (N=1,851)	Discontinued (N=871)	Did not discontinue (N=980)	p-value*
Female gender (N; %)	1,600 (86.4)	760 (87)	840 (86)	0.333
Age (in years; mean ± SD)	52.4±12.5	52.2±13.1	52.5±12.0	0.601
Years of education (mean ± SD) (n=1,233)	7.3±4.5	7.1±4.3	7.5±4.7	0.111
Current smokers (n; %) (n=1,486)	195 (13)	96 (13)	99 (13)	0.897
BMI (kg/m2) (mean ± SD) (n=1,146)	27.0±4.9	27.0±5.0	26.9±4.7	0.517
Age at diagnosis (years) (mean ± SD)**	44.1±13.3	43.8±13.6	44.4±13.1	0.356
Treatment delay (years)§ (mean ± SD)**	8.2±7.9	8.3±8.0	8.2±7.8	0.865
N. of Comorbidities† (mean ± SD) (n=1,512)	0.6±0.8	0.7±0.9	0.5±0.8	<0.001
RF positive (N; %) (n=1,596)	1,198 (75)	588 (76)	610 (74)	0.246
ACPA positive (N; %) (n=1,278)	949 (74)	465 (75)	484 (73)	0.381
Antibody positivity (RF and/or ACPA) (N; %) (n=1,543)	1,323 (86)	648 (87)	675 (84)	0.223
Swollen joint count (28) (mean ± SD) (n=1,219)	8.0±5.5	8.2±5.5	7.8±5.5	0.240
Tender joint count (28) (mean ± SD) (n=1,219)	10.6±7.5	11.1±7.6	10.2±7.3	0.028
DAS28-ESR(4) (mean ± SD) (n=1,058)	5.6±1.3	5.8±1.3	5.5±1.3	0.006
HAQ (mean ± SD) (n=940)	1.46±0.65	1.57±0.65	1.38±0.64	0.001
ESR in mm/h (mean ± SD) (n=1,173)	37.6±25.8	39.6±25.9	35.8±25.5	0.012
CRP in mg/dL (mean ± SD) (n=1,076)	2.2±3.0	2.2±2.8	2.2±3.1	0.983
csDMARDs (N; %)	1,617 (87)	773 (89)	844 (86)	0.090
Oral glucocorticoids (N; %)	1,266 (68)	616 (71)	650 (66)	0.042
bDMARD¥				
TNF inhibitors	1618 (87)	769 (88)	849 (87)	<0.001
Non TNF inhibitors	233 (13)	102 (12)	131 (13)	

*Independent samples t-tests for continuous variables and Chi-squared test for dichotomous variables**missing data <10%; †Comorbidities: cardiovascular diseases including arterial hypertension, chronic respiratory diseases, chronic renal disease, psychiatric diseases, Diabetes Mellitus and thyroid dysfunction §Time from RA diagnosis until treatment initiation ¥ TNF inhibitors: adalimumab, certolizumab, etanercept, golimumab, infliximab; non TNF inhibitors: abatacept, anakinra, rituximab, tocilizumab. ACPA-anti-citrullinated protein antibodies; BMI- body mass index; CRP- C-reactive protein; ESR- erythrocyte sedimentation rate; HAQ- health assessment questionnaire; RA-rheumatoid arthritis; RF- rheumatoid factor; TNF- tumour necrosis factor; SD-standard deviation.

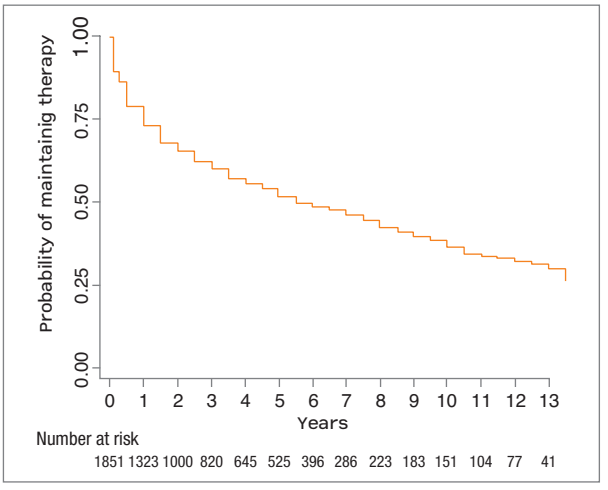

FIGURE 1. Kaplan-Meier annual persistence estimates for first-line biologic therapy

Portuguese RA patients is relatively high (5.5 years) when compared with other European RA cohorts[13,26,40,41]. This fact could possibly be explained by better therapeutic responses in Portuguese RA patients due to unknown socioeconomic, demographic or clinical factors, by lower patient expectations or by different perceptions on treatment targets. Nevertheless, further research into this topic should be performed, namely through multinational observational studies, directly comparing bDMARD discontinuation in different countries[42].

In line with previous studies, inefficacy was the leading cause of discontinuation[36]. Predictors of increased likelihood of therapy discontinuation were higher baseline HAQ, higher number of comorbidities, starting therapy from 2007 onwards, being treated with non-

TABLE II. REASONS FOR bDMARD DISCONTINUATION

	Discontinued N=871
Inefficacy	476 (54.6%)
Adverse event	262 (30%)
Allergy	49
Infection	38
Haematological disturbances*	13
Abnormal liver function tests	6
Cancer	4
Other AE**	15
Unspecified	137
Other	69 (7.9%)
Surgery	25
Remission	18
Patient decision	14
Pregnancy/Pregnancy planning	7
Death (not related to therapy)	5
Unknown	64 (7.3%)

*Leukopenia, neutropenia or anaemia; **Gastrointestinal disturbances, psoriasis, vasculitis, demyelinating disease, lupus-like syndrome, cardiovascular diseases.

-TNFi and having higher DAS28 scores during follow--up visits.

An increase in one unit in baseline HAQ is associated with an increased likelihood of therapy discontinuation of 39%. Interestingly, when analyzing this variable over time, no association was found, suggesting that avoiding disability before, rather than after bDMARD initiation yields better outcomes. The relationship between baseline HAQ and increased discontinuation was previously described[19, 31], but this is the first study to evaluate this predictor in a large cohort for a long period of time.

Starting bDMARD therapy from 2007 onwards was associated with an increase in therapy discontinuation by 89%, which is not unexpected and probably reflect the introduction of new therapeutic options with different modes of action for patients not responding adequately to the first-line TNFi[35,40,43]. Similarly, patients with higher number of comorbidities at the time of therapy initiation were at increased risk of bDMARD discontinuation by 17%, which can be possibly explained by the higher rate of clinical adverse events leading to discontinuation in this population[44]. This suggests that the control of associated comorbidities before starting therapy may improve persistence.

Receiving treatment with TNFi in comparison with a non-TNFi was associated with a 26% decrease in the likelihood of discontinuation. However, this finding must be interpreted with caution. Of note, and expectedly, there were significantly fewer patients starting a non-TNFi as a first-line therapy than those starting a TNFi and they most likely differ both on measured and unmeasured factors, making a direct comparison difficult to interpret (i.e. effect size 'blurred' by possible 'cofounding by indication'). Nonetheless, the scarce available literature is in-line with our results[40].

The time-varying model assesses clinical variables over time, enabling the identification of factors associated with therapy ceasing during follow-up. This model allows for the analysis of data otherwise excluded from the baseline model. For example, baseline DAS28 was not found to associate with bDMARD discontinuation, but when analyzed sequentially during follow-up higher values (i.e. higher disease activity), obviously, predicted bDMARD discontinuation.

Our study has several strengths but also important limitations. This was a large prospective observational study with long follow-up that allowed us to evaluate the possible association of several sociodemographic and clinical characteristics and bDMARDs discontinuation, in a 'real world' setting which easily translates to clinical practice. The long study period ranging from the beginning of TNFi bDMARD use in Portugal to the era where drugs with multiple modes of action are availability yields relevant insights to the practicing clinician. On the other hand, some of our findings (e.g. the difference between TNFi and non-TNFi as highlighted above) are most likely driven by bias (i.e. prognostic dissimilarity) due to the lack of randomization. In the setting of our study, i.e. clinical practice, previous experience (and believes) of the treating rheumatologist as well as patients' expectations, most likely, largely influence prescription patterns and outcomes. Finally, as in any other clinical cohort, the amount of missing data was not negligible. However, to handle information bias (to the extent possible), researchers from each center completed (when possible) the central database by reviewing the local clinical records.

CONCLUSION

Portuguese RA patients remain on their first-line bio-

TABLE III. PREDICTORS OF FIRST-LINE bDMARD DISCONTINUATION (MULTIVARIABLE ANALYSIS)

	Baseline Model Multivariable analysis N=824 HR (95% CI)	Time-Varying Model Multivariable analysis N=1,512 HR (95% CI)
Female (ref: male)*	1.06 (0.78-1.44)	1.02 (0.79-1.34)
Age (years)*	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Current Smoking (ref: non-smoker)*	‡	‡
Start biologic therapy ≥ 2007*	1.34 (1.01-1.78)	1.89 (1.50-2.38)
Number of Comorbidities*	1.13 (1.01-1.28)	1.17 (1.05-1.29)
TNF inhibitor (ref: non-TNFi)*	‡	0.74 (0.57-0.94)
Seropositive (RF and/or ACPA) (ref: seronegative)*	†	†
Oral glucocorticoids**	‡	‡
Concomitant csDMARD**	†	†
HAQ**	1.39 (1.17-1.64)	‡
Painful joint count**	¥	¥
Swollen joint count**	¥	¥
DAS28**	1.09 (1.02-1.17)	1.08 (1.06-1.10)
CRP mg/dL**	¥	¥
ESR mm/h**	‡	‡

*Baseline variables; **Time-varying variables; †variable not selected during univariable analysis (p>0.20); ‡ Variable not selected during multivariable analysis (p>0.05); ¥ variable not selected due to collinearity
Other variables not selected during univariable analysis (p>0.20): years of education, body mass index (BMI), age at RA diagnosis, time from diagnosis until therapy and pain, patient and physician VAS.
HR: hazards ratio; ACPA: anti-citrullinated protein antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: health assessment questionnaire; RA: rheumatoid arthritis; RF: rheumatoid factor

logic therapy for relatively long periods. However, the introduction of novel therapeutic options in 2007 decreased this persistence. Patients are at increased risk of discontinuing first-line bDMARD if they have higher disability and more comorbidities. This study provides a detailed view into biologic therapy discontinuation and it s predictors in the Portuguese RA population, delivering important information to clinicians in order to optimize bDMARD use.

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